REMARKS

Reconsideration of the present Application in view of the following remarks is respectfully requested. Claims 1, 3-5, and 8-16 are currently pending, and claim 1 is amended herewith solely by adding clarifying punctuation. The PTO has withdrawn claim 14 from consideration pursuant to 35 C.F.R. § 1.142(b), asserting that that the claim is directed to a non-elected species.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 1, 3-5, 8-13, and 15-16 stand rejected under 35 U.S.C. § 103(a), for alleged obviousness over Tonks et al. (WO 98/04712, " '712") in view of Flint et al. (*Proc. Natl. Acad. Sci. USA* 94:1680-1685, 1997) and U.S. Patent No. 5,804,395 (Schade et al.), and also for alleged obviousness over Tonks et al. (U.S. Patent No. 5,912,138, " '138") in view of Jia et al. and Schade et al. (In the latter rejection no further mention is made of Jia et al. while Flint et al. are again raised in the PTO's discussion; hence the disclosure of Flint et al. is herein addressed.) The PTO alleges that a person having ordinary skill in the art would have found it obvious to arrive at the claimed method of identifying an agent that alters the interaction between the substrate trapping mutant protein tyrosine phosphatase (PTP) of Tonks et al. ('712 or '138) or Flint et al. by measuring a fluorescent polarization signal as taught by Schade et al. The PTO further asserts that fluorescence polarization assays are routinely used to measure enzymatic activity and that therefore an ordinarily skilled person would have been motivated to use fluorescent polarization signals to monitor the interaction between the PTP and its substrate with a reasonable expectation of success.

Applicants respectfully traverse this rejection and submit that the documents cited by the PTO, whether alone or in combination, fail to teach or suggest the subject matter of the instant claims. Briefly, and for reasons elaborated upon below, the cited art with respect to fluorescent polarization (FP) assays fails even remotely to contemplate the use of FP in a substrate trapping modality, *i.e.*, in a context where *enzyme catalytic activity* is <u>not</u> being determined, and in particular where an FP signal generated by a PTP substrate further to its

interaction with a substrate trapping mutant PTP is involved. Therefore, contrary to the PTO's assertions, well known assays of *enzyme catalytic activity* are beside the point in the presently claimed assay methods, which employ *catalytically attenuated* mutant PTPs referred to as substrate trapping mutant PTPs. The PTO errs further in asserting that the Tyr46 mutant PTP of Flint et al. is a substrate trapping mutant according to the present invention. It is not, and in any event, nowhere do Flint et al. or either of the Tonks et al. documents in any way suggest the application of FP assays, which were previously known to the art for determining enzyme catalytic activity, to the instant methods for screening agents by using *catalytically inactive* substrate trapping mutant PTPs.

The PTO has not established a *prima facie* case of obviousness. *See In re Mayne*, 104 F.3d 1339, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (PTO has the burden of showing a *prima facie* case of obviousness.). The PTO must show (1) that the combined references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. When rejection of claims depends upon a combination of prior art references, something in the prior art as a whole must suggest the desirability, thus the obviousness, of making the combination (*see In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998)).

Applicants respectfully submit that a *prima facie* case of obviousness has not been established because the cited documents fail to teach or suggest each and every limitation of the claimed method. Each document, alone or in combination, fails to teach or suggest a method for identifying an agent that alters the interaction between a PTP and a tyrosine phosphorylated polypeptide that is a substrate of the PTP, comprising in pertinent part (a) contacting in solution in the absence and presence of a candidate agent a substrate trapping mutant PTP and a phosphorylated peptide substrate that is capable of generating a FP signal under conditions that permit formation of a complex between the peptide substrate and the substrate trapping mutant

PTP, and (b) comparing in solution, without separating the complex from free substrate, the FP signal level in the absence of the agent to the FP signal level in the presence of the agent.

Applicants agree with the PTO that Tonks et al. '712 and '138 both fail to teach or suggest detecting the interaction between a PTP and its substrate in solution by measuring FP signals. None of the cited documents, alone or in combination, teaches or suggests using a phosphorylated PTP substrate that is capable of generating a FP energy signal in a FP assay. Neither does any one or more of the documents cited by the PTO teach or suggest contacting a substrate trapping mutant PTP with a phosphorylated peptide substrate under conditions that permit formation of a complex in solution, and then comparing, in solution, the FP energy signal in the absence and presence of a candidate agent. Moreover, Flint et al. and Schade et al. fail to teach or suggest any assay to identify an agent that alters the interaction between a substrate trapping mutant PTP and a PTP peptide substrate. Schade et al. provide nothing more than a cumulative reference in view of those cited in the instant specification that describe FP as a known method. Schade et al. merely disclose an assay for measuring enzymatic activity of a protease by measuring fragments of substrate that are cleaved by the protease, but Schade et al. nowhere contemplate a FP assay that does not report enzymatic activity. Schade et al. certainly fail in any way to suggest adapting FP assay methodology to substrate trapping mutant PTPs.

The PTO concedes that Tonks et al. '712 and '138 both fail to teach or suggest a human PTP1B in which the tyrosine at position 46 is substituted with a phenylalanine residue. The PTO alleges, however, that Flint et al. teach several substrate trapping PTPs including a mutant PTP1B that comprises a mutation at Tyr46. Applicants respectfully submit that Flint et al. do not teach "several" substrate trapping mutant PTPs, and Flint et al. do <u>not</u> teach that a mutant PTP1B in which the Tyr46 is substituted with serine or leucine is a substrate trapping mutant.

As disclosed in the present application, according to certain embodiments a substrate trapping mutant PTP is derived from a wildtype PTP that has been mutated such that the wildtype PTP catalytic domain invariant aspartate residue is replaced with an amino acid that does not cause significant alteration of the Km of the enzyme but results in a reduction in Kcat to less than 1 per minute. Such a mutant PTP may have, *in addition*, a wildtype tyrosine residue

replaced with an amino acid that is not capable of being phosphorylated (*see, e.g.,* specification at page 16, lines 4-8; page 18, lines 12-18; page 19, line 26 through page 21, line 5).

Flint et al. fail to teach or suggest a substrate trapping mutant PTP1B that has a substitution of the invariant aspartate residue *and* substitution of a wildtype tyrosine residue such as Tyr46. Flint et al. describe a single PTP1B substrate trapping mutant in which the invariant aspartate residue at position 181 is substituted with alanine, which mutant PTP1B exhibits significantly reduced catalytic activity (Kcat decreased by approximate 10^5) but retains the ability to bind substrate (*see* Flint et al., page 1681, column 2; Table 1). By contrast, substitution *only* of Tyr46 in the wildtype PTP1B polypeptide, as described by Flint et al., results in a mutant PTP1B that is not a substrate trapping mutant PTP according to the instant claims. The Tyr46-substituted PTP1B mutant of Flint et al. has a significantly *weakened* affinity for substrate (Km increased approximately 20-fold); thus, such a mutant would not effectively trap substrate (*see* Flint et al., page 1681, column 2). Therefore, the PTO errs in its assertion that by providing a mutant PTP comprising a mutation at Tyr46, Flint et al. teach a substrate trapping mutant.

Furthermore, Tonks et al., Flint et al., and/or Schade et al. fail to provide the requisite teaching, suggestion, or motivation for a skilled artisan to modify the documents' respective teachings to obtain Applicants' invention. As discussed above, Flint et al. and Schade et al. are silent with respect to performing any assay to identify an agent that alters the interaction between a substrate trapping mutant PTP and a PTP peptide substrate. Moreover, and contrary to the assertion by the PTO, Tonks et al. and/or Flint et al. lack any teaching or suggestion that a person having ordinary skill in the art would recognize the desirability of modifying the disclosures therein in view of the teachings of Schade et al. As also noted above, the disclosure of Schade et al. relates to an assay for measuring *enzymatic activity* by FP, but fails to suggest combining the assay methods described therein with *any* enzyme that has been catalytically attenuated by specific mutation, much less to combine an FP assay with the substrate trapping mutant PTP as presently recited.

Therefore, absent the teachings of the present application, a person having ordinary skill in the art would not have been motivated to arrive at an FP-based agent screening assay using substrate trapping mutant PTPs, which have *significantly reduced catalytic activity*

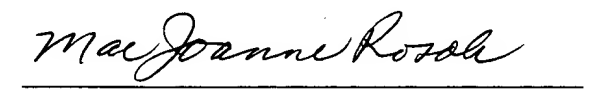
(Tonks et al. (U.S. Pat. No. 5,912,138 at column 1, lines 44-56; column 2, lines 36-53; Flint et al., page 1681, column 2 and Table 1). Applicants therefore respectfully submit that the presently claimed invention is not obvious over the combined teachings of Tonks et al. ('712 and '138), Flint et al., and Schade et al., and that at the time of filing the instant application, a person having ordinary skill in the art could not reasonably have expected successfully to achieve Applicants' invention.

Accordingly, Applicants respectfully submit that a *prima facie* case of obviousness has not been established and that the claimed invention satisfies the requirements of 35 U.S.C. § 103. Applicants therefore request that the rejection of the claims be withdrawn.

Applicants respectfully submit that all claims remaining in the Application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. In the event that the Examiner believes a teleconference will facilitate prosecution of this case, the Examiner is invited to telephone the undersigned representative at (206) 622-4900.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



Mae Joanne Rosok
Registration No. 48,903

Enclosures:
Petition for Extension of Time
Postcard

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

521327_1